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Review Article

Cladribine in First Line and Relapsed Hairy Cell Leukemia and the Hairy Cell Leukemia Variant

Marlies Van Hoef[1]* and Xavier Troussard[2]

[1]*Dept of Medical Affairs, Lipomed AG, Fabrikmattenweg 2/4, 4144 Arlesheim, Switzerland*
[2]*Dept of Hematology, University Hospital, Avenue de la Cote de Nacre, CS 30001, 14033 Caen Cedex 9, France*

***Address for Correspondence:** Marlies Van Hoef, Lipomed AG, Fabrikmattenweg 2/4, 4144 Arlesheim, Switzerland, Tel: +0041-61-715-9651; E-mail: vanhoef@vanhoefconsulting.com

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ABSTRACT

Hairy cell leukemia is a rare disease for which purine nucleoside analogues changed disease outcome. Pentostatin and 2-chorodeoxyadenosine (cladribine) have meanwhile been administered since over two decades. The former compound is available for intravenous administration and the latter for both intravenous and subcutaneous administration. Cladribine induces high response rates in first line purine nucleoside analog treatment, regardless of prior treatment with splenectomy, interferon or chemotherapy, and is also effective in relapsed disease. Literature describing the use of cladribine upfront and in later lines of treatment in hairy cell leukemia and the hairy cell leukemia variant is reviewed herein.

Keywords: Hairy cell leukemia (variant); Cladribine; Rituximab; First line; Relapsed

INTRODUCTION

Hairy Cell Leukemia (HCL) is a rare disease that represents 2% of adult leukemia. Classical HCL is a B-cell chronic lymph proliferative disorder characterized by splenomegaly, pancytopenia and bone marrow involvement with fibrosis and occurs at a median age of 52 years [1]. Due to earlier detection currently common symptoms are fatigue and infection, while splenomegaly is often absent. HCL variant (HCLv) is an uncommon disorder, distinct from classical HCL that accounts for about 10% of all HCL cases. The BRAF V600E mutation has been reported in the majority of patients with classical HCL but not in HCLv, which may explain the clinical observation that HCLv follows a different clinical course and response to therapy [2,3].

Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analog that was developed in the 1970s. It was first tested in humans in the early 1980s and became an established product for the treatment of hairy cell leukemia. Cladribine is a chemotherapeutic compound that can be administered intravenously or subcutaneously. It is a pro-drug that is activated after uptake in cells [4]. It functions as an antimetabolite and is toxic in hematopoietic cells and leukemic and lymphatic malignancies, but has little or no effect in non-hematopoietic tissues and solid tumors. It is polyvalent and is toxic for dividing and quiescent cells [4]. Cladribine induces myelo suppression and immunosuppression.

The clinical practice guidelines for treatment of hairy cell leukemia recommend the purine nucleoside analogs cladribine or pentostatine for first line treatment and dependent on the time of relapse after treatment either retreatment with a purine nucleoside analog alone or in combination with rituximab [5,6]. In refractory disease combination of a purine nucleoside analog with rituximab or alternative treatment is recommended. A review of the efficacy of cladribine in hairy cell leukemia and the hairy cell leukemia variant is described in this paper.

REVIEW

Publications with over 50 patients with HCL treated with cladribine

Table 1 provides an overview of studies that included 50 or more patients with HCL, who received treatment with cladribine.

Saven et al. [7] reported 358 patients; 349 were evaluable for response. After a single course of cladribine 319 (91%) achieved a complete response and 22 (7%) a partial response for an overall response rate of 98%. Ninety of patients with response relapsed; complete responders at median 30 months and partial responders at median 24 months. The median time to first relapse was 29 months. After first relapse 63 patients were retreated with cladribine; for 53 information is available. Thirty three patients (62%) achieved a complete response and 14 (26%) a partial response for an overall response rate of 88% in second line. At the time of the report (58 months follow-up form start of first treatment) 19 patients had experienced a second relapse. Seven of these patients were retreated and two obtained a complete response and four a partial response for an overall response rate of 86% in third line. The time to treatment failure for first line responders was 6.5% at 24 months (complete responders 5.3% and partial responders 21.5%) and 18.7% at 48 months (complete responders 16.3% and partial responders 53.7%). Overall survival for first line complete responders was 99.7% at 24 months and 98.3% at 48 months. Survival for first line partial responders was 96% at 24 months and 91.8% at 48 months.

Robak et al. [8] reported 103 patients treated with intravenous cladribine administered over 2-hours for 5 consecutive days. Complete remission was achieved in 75 patients (77.3%) after one to three cycles of cladribine; 53 patients received one, 16 patients two and 6 patient three cycles. The overall response rate was 95.9%. Cladribine was equally effective in newly diagnosed as in pretreated patients, who had received splenectomy, prednisone, chlorambucil and/or interferon alpha. Twenty patients obtaining complete response relapsed after a mean duration of response of 32 months; 17 of 20 patients relapsed after one cycle and only 3 patients after two or three cycles. Ten relapsed patients were retreated with cladribine and ten were in stable partial response and required no second line treatment. Seven patients obtained a second complete response and three a partial response for an overall response of 100% in second line. The mean duration of second response was 19 + months.

Dearden et al. [9] reported 165 patients who received pentostatine and 45 patients who were treated with cladribine, of whom 12 had not received prior treatment. The complete response rate in patients who received cladribine in first line was 84.4% and the overall response rate was 100%. Four patients initially obtaining partial response received a second cycle of cladribine to achieve complete remission, the other patients had received one cycle. Seventeen of relapsing patients were retreated with cladribine; 13 patients obtained a complete response and 4 patients a partial response. For those who initially received a complete remission the five years overall survival was 97%.

The other authors had administered cladribine to newly diagnosed or pretreated patients at doses of 0.09, 0.1, 0.12 or 0.14 mg/ kg/ d i.e. over 2 hours for five days, as continuous infusion for seven days, or on day one of six consecutive weeks [10-15]. Complete remission rates varied from 72% to 94% in first line cladribine administration and no relationship to the dose of administration was definable. Response to treatment was independent of pretreatment. Overall response rates varied from 93% to 100%. In case patients had not obtained complete response after the first cycle of cladribine, one or more additional cycles were administered [11,15]. The interval between cycles was 4 to 6 months [11]. Rosenberg et al. Reported high complete remission

Table 1: Publications with over 50 patients with hairy cell leukemia treated with cladribine.

Author	Pretreat-ment	Treatment with cladribine	Patients	ORR 1st line	ORR 2nd line	ORR 3rd line	DFS/PFS	OS	Commend
[7] Saven A	Splenecto-mie, INF, 2-DCF	0.087 or 0.1 mg/ kg/ d iv continuous 7d	358, 349 evaluable, 129 untreated	CR 319 (91%) ORR 341 (98%)	CR 33/53 (62%) ORR 47/53 (88%)	CR 2/7 (28%) ORR 6/7 (86%)	At median 29 m RFS 74%	At median 39m 94%	
[8] Robak T	Splenecto-mie, IFN-alpha ± prednison. Prednison/ chlorambu-cil/cyclo-phosphami-de	0.12 mg/ kg/ d 2h infusion for 5d	56 HCL new 41 HCL relapsed 6 HCLv	CR 75 (77.3%) PR 18 (18.6%) ORR 95.9%	CR 7/10 PR 3/10 ORR 100%		Mean 1st DOCR 32 (3 - 72m) First relapse in 20/75 with mean PFS 37.4 (10-66) Mean 2nd DOCR 19 + (8-47) m		In 1st line CR in 53 pat after 1 cycle, in 16 pat after 2 cycles, in 6 pat after 3 cycles
[9] Dearden CE	Splenecto-mie, IFN ± sple-nectomie	0.1 mg/ kg/ d iv continuous 7d	165 pentost, 38 untreated 45 cladribine, 12 untreated	CR p 82% PR p 15% CR c 84.4% PR c 15.6%	CR 5/8 PR 2/8 CR 13/17 PR 4/17		At 71 m 40, 24% relapsed At 45 m 13, 29% relapsed	At 5 yr 97% for those who achieved CR	In 1st line in 4 PRs a 2nd cycle cladribine given
[10] Robak T		0.12 mg/ kg/ d iv 2 hr 5d, or 0.12 mg/ kg/ d iv 1d, 6 weeks	116 untreated	CR 47 (76%) PR 12 (19%) CR 39 (72%) PR 10 (19%)			Median 4.3y Median 5.1y	6.5y 91% 6.5y 88%	97 pat (84%) received 1, 19 2 or more courses
[11] Else M		0.1 mg/ kg/ d iv continuously for 7d	188 pentost 45 cladribine, likely untreated	CR p 82% CR c 76% ORR p 96% ORR c 100%	13/24 CR 54% 39/51 CR 76% ORR p 92% ORR c 100%	3/3 CR 100% 5/13 CR 38%	1st line med RFS 16y 2nd line med RFS 11y 3rd line med RFS 6.5y		CR equally durable in1, 2, 3rd line. 2nd cycle given to 8 pat if no CR after 1st cycle -> 6 CR
[12] Rosenberg JD	Splenecto-Mie ± IFN IFN ± sple-Nectomie ± Choram -bucil 2-DCF	0.1 mg/ kg/ d iv continuous 7d	88 young pat, 83 evaluable	CR 72 (88%) PR 10 (12%) ORR 100%	Info for 27 of 31. CR 12 (44%) PR 6 (22%) CHR 8 (30%)	CR 1 (20%) PR 4 (80%)	Med 1st DOR 57m Med time to 1st relapse in 58% 54m Med 2nd DOR 30m in all responders	For CRs med 238m For PRs med 122 m	Single courses of cladribine in young pat induced high CR rate
[13] Hacioglu S		0.14 mg/ kg/ d or 0.09 mg/ kg/d for 5 or 7 d continuously iv	78, likely untreated	CR 63 (80.7%) PR 13 (16.6%) ORR 97.3%	CR 13/19 (68.4%) PR 6/19 (31.5%)	CR 2/3 (66.6%) PR 1/3 (33.3%)	Rel rate 16.6% CR med TTR 36m, PR med TTR 6m 2nd rel rate 31.5%, med TTR 60m	25m med OS 96% 228m med OS 82.8% 5y OS 96%	
[14] Khorsid O	Splenecto-mie, IFN, ChT	1.1 mg/ kg/ d iv 7d vs 0.14 mg/ kg/ d sc 5d	49 pat. 41 untreated, 18 i.v., 31 s.c.	CR i.v. 94% CR s.c. 97%			Med EFS i.v. 53m, s.c. 63m 3y EFS i.v.: 60% s.c.: 96%	Med OS i.v. 74m, s.c not reached 3y OS i.v. 81%, s.c. 100%	In s.c. group 4 achieved CR after 2 cycles
[15] Von Rohr	Splenec-tomie, RT, ChT, IFM alpha ± ChT	0.14 mg/ kg/ d s.c. 5d	33 untreated 15 relapsed 14 with PD	CR 47 (76%) PR 13 (21%)			At 3.8 yr 7 progressions after PR, 8 relapses after CR. Median TTF was 38 m for all pat	At 1 yr 97% At 2 yr 93%	2 pat with PR after 1st cycle received one and two cycles more and got CR and PR by 0.1 mg/kg/d iv 7d

IFN = Interferon; 2-DCF = 2-Deoxycoformycine; RT = Radiotherapy; ChT = Chemotherapy; ORR = Overall Response Rate; CR = Complete Response; PR = Partial Response; DFS/PFS = Disease Free or Progression Free Survival; DOCR = Duration of Complete Response; DOR = Duration or Response; TTF = Time to Treatment Failure; TTR = Time to Relapse; EFS = Event Free Survival; OS = Overall Survival; Pentost = Pentostatin.

rates after single courses of cladribine in young patients [12]. Median reported duration of response was 57 months [12] and median event free survival 53 months [14]. Others reported median progression free survival of 4.3 and 5.1 year [10] and a relapse free survival of median sixteen years [11]. The median time to treatment failure was much longer in patients who had obtained complete response than those with partial response [13]. Median overall survival at 5 years exceeded 90% [10, 13]. Moreover median overall survival was much longer for patients who had obtained complete response, than those with partial response [13]. Complete response rates of

44% to 76% were also reported when patients were retreated with cladribine in second line after first relapse [11-13]. Overall response rates in second line varied from 66% to 100%. Some authors reported administration of cladribine after second relapse in third line [11-13]. Complete response rates in third line varied from 20% to 66.6% and overall response rates were 100% [11-13]. Complete responses in first to third line of treatment were of equal duration, but duration of responses progressively decreased with the increase of the line of treatment due to shorter partial responses (11). Rosenberg et al. reported two patients who received fourth line cladribine [12]; one patient obtained a complete response but relapsed after 3 months; he received fifth line cladribine and obtained again a complete response; the other patient had no response to fourth line cladribine. Von Rohr et al. and Khorsid et al. described the administration of 0.14 mg/ kg/d subcutaneously for five days [14,15]. Complete response rates were 76% and 97% respectively and Von Rohr reported and overall response rate of 97%. Median time to treatment failure was 38 months and median event free survival was 63 months respectively. Von Rohr et al. reported 93% overall survival at two years [15]. Khorshid et al. compared intravenous with subcutaneous administration and reported event free survival of 60% and 96% respectively and three years overall survival of 81% and 100% respectively [14]. Both author considered five days subcutaneous administration an excellent alternative to intravenous administration.

Publications reporting 25 to 49 patients treated with cladribine

Table 2 provides an overview of studies that included Cladribine was administered to newly diagnosed or pretreated patients at doses of 0.09, 0.1, 0.14, 0.15 mg/ kg/ d either as 2-hour infusion for 5 days or continuous intravenous infusion for 7 days or a 4 mg / m2 continuous intravenous administration for 7 days [16-21,23]. Zinzani et al. compared consecutive 2-hour infusions for 5 days with infusions on day one of 5 consecutive weeks and found no difference in outcome [22]. Complete response rates varied from 76% to 98% [16-19,21-23]. Patients in partial remission obtained a second cycle to achieve complete remission and few required more than two cycles [16, 18]. Damasio et al. was the only author who reported lower complete response rates at 3 months (26.3% and 35.3% dependent on infusion schedule) and observed, just as others, that 2-hour infusions for 5 days induced comparable overall response rates to continuous infusions for 7 days [20]. Tallman et al. reported an increase of complete response rate from 80% at three months to 90% at six months [16]. Damasio et al. reported an increase in overall response rates from 3 to 6 months, which were dependent on infusion type (2-hour 5 days) 84.2% and 88.8% respectively and (continuous 7 days) 76.5% and 81.2% respectively [20]. These reports support the observation that response develops slowly over time in HCL. Overall response

Table 2: Publications reporting 25 to 49 patients with hairy cell leukemia treated with cladribine.

Author	Pretreatment	Treatment with cladribine	Patients	ORR	DFS/PFS	OS	Commends
[16] Tallman MS	Splenectomie, IFN-alpha, Splenectomie ± IFN-alpha ± 2-DCF	0.1 mg/ kg/ d continuous iv 7d	26, 15 untreated	CR 16/20 (80%) 3m PR 4/20 (20%) CR 18/20 (90%) 6m	12m DFS in CR 100%, 1 pat with PR relapsed		3 PRs 2nd cycle of cladribine -> 2 CR
[17] Seymour JF	Splenectomie, INF ± splenic-tomie	4mg/ m2 continuous iv 7d	46, 21 pretreated	CR 36 (78%) PR 5 (11%)	3y RFS 77%		2 pat 2nd line cladribine -> both PR
[18] Robak T	Splenectomie, INF-alpha, both	0.1 mg/ kg/ d iv 2h 5d, vs continuous 7d iv 5 pat received 0.05 mg/ kg/ d	41, 23 2h iv, 18 continuous iv, 25 pretreated, 16 untreated	CR 31 (76%) PR 9 (22%)	Mean DOR 25.2m		CR rate after 5d course 75%, after 7d course 76% CR rate 82.6% after 2hr and 66.7% after continuous infusion
[19] Hoffman MA	Splenectomie, INF ± splenic-tomie	0.1 mg /kg/ d continuous 7d	49, 28 pretreated	CR 37 (76%) PR 12 (24%)	At 55m RFS 80%	At 55m OS 95%	6 pat 2nd line cladribine, 3 CR and 3 PR
[20] Damasio EE		0.15 mg/ kg/ d 2h iv 5d vs 0.1 mg/ kg/ d continuous iv 7d	22 19 All likely untreated	CR 5/19 (26.3%) 3m PR 11/19 (57.9%) CR 6/17 (35.3%) 3m PR 7/17 (41.2%)			At 6m ORR 88.8% At 6m ORR 81.2%
[21] Jehn U	Splenectomie ± IFN-alpha ± 2-DCF	7d continuous iv	42, 10 pretreated	CR 41 (98%) PR 1 (2%)	At 6y DFS 75%		3 relapsed pat retreated, all 2nd CR
[22] Zinzani		0.14 mg/ kg/ d 2h iv 5d, vs 0.14 mg/ kg/ d 2h iv 1d for 5week	21 untreated 16 untreated	CR 30 (81%) PR 7 (19%)	At 122m 8 relapsed, 4 out of either subset 13y RFS 52%	13y OS 90%	8 pat 2nd line cladribine -> 6 CR, 2 PR; med DOR 58m
[23] Somasundaram		0.09 mg/ kg/ d continuous iv 7d	27 likely untreated	CR 25 (93%) PR 2 -> CR after 2nd cycle	At 26m 5 pat relapsed	Med OS 26m	5 pat 2nd line cladribine, all again CR

INF = Interferon; 2-DCF = 2-Deoxycoformycine; ORR = Overall Response Rate; CR = Complete Response; PR = Partial Response; DFS = Disease Free Survival; PFS = Progression Free Survival; RFS = Relapse Free Survival; DOR = Duration of Response; OS = Overall Survival.

rates varied from 76.5% to 100% [16-23]. Relapse free or disease free survival was reported as 100% at 12 months [16], 77% at three years [17], 80% at five years [19], 75% at six years [21] and 52% at thirteen years [22]. Cladribine in second line induced complete response rates varying from 0 to 100% with the majority of authors reporting > 50%, and overall response rates of 100% [16,17,19,21-23]. A median duration of second response of 58 months was reported by Zinzani et al. [22]. Overall survival was reported as median 26 months, 95% at 55 months and 90% at 13 years [19,22,23].

Publications reporting treatment for patients with HCLv

Table 3 provides an overview of studies that reported patients with HCLv, who received cladribine (containing) treatment.

HCLv is a very rare disease and the number of patients reported were small. Cladribine alone was administered at a dose of 0.09, 0.1 of 0.12 mg/ kg/ d as five days two hour or as seven days continuous infusion [8,24-26]. In two publications a partial response of 33% was reported with no complete responses [8,26]. In two other publications a complete response of 25% and 33% and an overall response of 75% and 100% were reported [24,25]. Treteault et al. performed splenectomy after administration of cladribine [24]. Robak et al. reported partial responses lasting 29 + and 60 + months [8]. Palomera et al. reported overall survival of 5 + , 9 + and 30 + months [25]. The response to cladribine alone is much lower in HCLv, than in HCL, and cladribine alone is not considered and efficient treatment. In contrast, the combination of cladribine with concurrent or sequential rituximab results in high response rates; complete response rates of 86% to 100% were reported [27-29]. Disease free survival was reported as not reached at median twenty five months [27], 80% at twenty seven months [28] and 64.3% at five years [29]. The last author reported and overall survival of 51% at five years [29]. One patient relapsed and was retreated with the same regimen of cladribine followed by rituximab [29]. Noteworthy is that patients die from second tumors and not from the HCLv after treatment with cladribine and rituximab [27,29]. Second tumors are considered to occur due to the underlying immune system disorder and not secondary to the therapy.

DISCUSSION

Cladribine is an effective treatment for hairy cell leukemia. Patients generally obtain a complete response after one cycle of treatment administered either as intravenous infusion for 5 or 7 consecutive days or as subcutaneous injection for 5 consecutive days [7-29]. Some patients require two and few three courses to obtain complete remission [8-11,14-16]. Complete responses reported exceed 75% and may reach over 90%, whereas overall response rates are generally over 90%. If more than one treatment course is required to obtain complete response, the courses are in general administered at least three months apart [11,16].

Retreatment with cladribine in case of relapse has been reported to occur up to five times and complete remission often occurs in second and third line of treatment [7-9,11-13,19,22,23]. Reported complete responses and overall survival among patients treated in second line vary from 44% to 76.4% and 86% to 100% respectively [7-9,11-13]; among patients treated in third line these vary from 20% to 66.6% and 86% to 100% respectively [7,11-13]. Complete responses have been reported to be of equal duration in second and third line,

Table 3: Publications reporting treatment for patients the with hairy cell leukemia variant.

Author	Pretreatment	Treatment with cladribine	Patients	ORR	DFS/PFS	OS	Commend
[8] Robak T	Splenectomie ± INF ± 2-DCF	0.12 mg/ kg/ d 2hr iv 5d	6	PR 2 (33.3%)	PR lasted 60 + and 29 + m		One of PRs had spelectomy, second PR received cladiribine every 6-12 m as maintenance
[24] Tetreault SA	1 pat received splenectomy after 2nd cycle cladribine	0.1 mg/ kg/ d continuous iv 7d, with repeat cycles	4	CR 1 (25%) PR 2 (50%)			Three pat had splenectomy after cladribine
[25] Palomera L	Splenectomie + INF-alpha	0.1 mg/ kg/ d continuous 7d	3, one pretreated	CR 1 (33%) PR 2 (67%)		9 + , 30 + , 5 + from treatment	
[26] Machii T	CHOP, INF, 2-DCF	0.09 mg/ kg/ d continuous 7d	3, one pretreated	PR 1 (33%)			
[27] Ravandi F	Not known if pretreated	5.6 mg/ m2 /d 2h 5d Rituximab 1 m later 375 mg/m2 8 wks	5	CR 5 (100%)	At 25 m med CR duration not reached, 1 relapse	40%	2 pat died from other tumors, relapsed pat died
[28] Kreitman RJ	Cladribine, Rituximab, Cladribine + ri-Tuximab + sple-nectomie	0.15 mg/ kg/ d 5d Rituximab from d1 375 mg/ m2 8wks	10, 2 untreated	CR 9 (90%) 6m	At med 27 m 8 pat (80%) remain free of MRD		
[29] Chihara D	none	5.6 mg/m2 iv 5d Rituximab 1 m later 375 mg/m2 8 wks	7	CR 6 (86%) 71% achieved MRD negative status	2 relapsed at 19 and 96 m after treatment 5y FFS 64.3%	5y OS 51.4%	1 relapsed patient retreated with same regimen, 2 pat died from other tumors, 1 from HCLv

IFN = Interferon; 2-DCF = 2-Deoxycoformycine; CHOP = Cyclophosphamide, Doxycline, Vincristine, Prednisone; ORR = Overall Response Rate; CR = Complete Response; PR = Partial Response; DFS = Disease Free Survival; PFS = Progression Free Survival; MRD = Minimal Residual Disease; FFS = Failure Free Survival; OS=Overall Survival.

although the time to relapse decreases as result of relapse in patients with partial remission, which results in progressively overall shorter time to treatment failure in subsequent lines of treatment [8,11,19].

Intravenous and subcutaneous administration are equally efficient, whereby the fact that subcutaneous administration only requires an injection, suggests that subcutaneous administration is highly cost-efficient compared to intravenous administration [14,15]. Complete responses appear to develop more gradually after subcutaneous than after intravenous administration, but this may depend on the dose of intravenously administered cladribine [11,14,22].

Although complete and overall response rates with pentostatin and cladribine are comparable, pentostatin needs to be administered intravenously for at least six cycles and is there with less convenient than intravenous or subcutaneous cladribine [9,11]. Secondary malignancies occur after both compounds and may be caused by a shared predisposition with HCL or be secondary to purine nucleoside analog treatment. Some authors reported the same frequency of second malignancies as in the general population, while Saven et al. reported an observed-to-expected ratio of 1.88 in 349 HCL patients treated with cladribine, but in this population there was a high rate (11.5%) of preexistent second malignancies [7,11,19,30].

The guidelines for treatment of HCL recommend interferon alpha, the BRAF inhibitor vemurafenib, the recombinant CD22-targeting immunotoxin moxetumomab pasudotox, Fludarabine plus rituximab, Bendamustine plus rituximab and cladribine plus rituximab for refractory HCL [5,6]. Interferon alpha was the first effective pharmacologic treatment for hairy cell leukemia [31]. The purine nucleoside analogs though replaced interferon alpha because of higher complete remission and invariable disease recurrence after cessation of interferon alpha [31,32]. Responses of short duration have been described when alpha interferon was administered upon relapse after cladribine [33,34]. Vemurafenib has been reported to induce complete response rates of 35% to 42% and overall responses including hematological response of 95% to 100% in refractory HCL [35,36]. Median relapse free survival varied from 9 to 17 months, and was longer in patients with complete compared to partial remission [35,36]. Secondary malignancies due to vemurafenib treatment though do occur [36,37]. A study with moxetumomab pasudotox in relapsed/refractory HCL after at least one prior purine nucleoside analog reported complete and overall response rates of 41% and 75% respectively and at 16.7 months follow-up a durable complete response rate of 30% [37]. Comparing this with complete and overall response rates reported for cladribine in second and third line and reported response durations, cladribine compares well to moxetumomab pasudotox [7-9,11-13,19,21-23,38,39]. No secondary malignancies were reported during the study, but follow-up is too short for evaluation of this condition [37]. Fludarabine and rituximab (four cycles) were reported to induce 100% overall response in thirteen of fifteen evaluable relapsed/ refractory patients after prior purine nucleoside analog therapy [40]. At median 35 months progression free survival was 93.3%, and at 5 years progression free and overall survival were 89% and 93% respectively. Bendamustine and rituximab (six cycles) were reported to induce 100% overall response with 58% complete response in twelve relapsed/refractory patients, of whom nine had responded to their last purine nucleoside analog therapy [41]. Response duration was shorter for partial than for complete responders and at median 31 months' six of seven complete responders were still in remission [41]. Cladribine and rituximab (one cycle) were reported to induce 100% complete response in relapsed patients, and 100% overall response with 89% complete response in relapsed/refractory patients after median two (range one to six) treatments with purine nucleoside analogs alone [29,42]. The failure free and overall survival at 5 years in the first publication were both 100%, and 94.4 % and 100% at median 36 follow-up in the second publication [29,42]. Thus when the response with cladribine or pentostatine alone in subsequent treatments is no longer satisfactory, cladribine and rituximab are and excellent alternative [42].

The results of treatment with cladribine as single agent in the HCLv are not as promising, but cladribine combined with or followed by rituximab is highly efficient, even in patients pretreated by cladribine, rituximab or the combination sequentially [8, 24-29]. This suggests that also the hairy cell leukemia variant can be retreated with cladribine and rituximab [28].

CONCLUSION

Cladribine is highly efficient in first line and relapsed HCL, and cladribine and rituximab in first line and relapsed HCLv.

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